NON-TECHNICAL ABSTRACT

We are proposing a gene therapy trial for Parkinson Disease (PD). Although we remain ignorant of the specific cause of PD, current understanding of what causes and what goes wrong in PD has focused on specific groups of cells deep in the brain. We know that the main problem in PD is that cells in the midbrain, which make the chemical signaling molecule (neurotransmitter) dopamine, die. By the time an individual develops the symptoms of PD, they have lost over 50% of these dopamine cells. As a result of this cell loss, the circuits in the brain that regulate the planning, initiation, smooth operation and termination of movements are "scrambled". Some cell groups in the circuit are overactive, some are underactive, but the endresult is an inability to execute normal movement. Hence, PD is best thought of as a disturbance in the activity of the cells in the brain that control movement. This leaves many potential targets for intervention, including drug strategies to boost dopamine (like taking Sinemet) as well as transplantation of dopamine cells, or strategies to block abnormally hyperactive brain regions by burning and destroying them or by implanting deep brain stimulation (DBS) electrodes which can inhibit brain activity. Despite substantial improvements in medical and surgical therapy for PD, all current treatment approaches either fail over time or have significant limitations or complications. Recent transplant or growth factor infusion studies have been disappointing, but of greater concern they also resulted in substantial adverse effects. One problem with aggressive experimental strategies is that they might work best on patients who are in early stages of their disease, but since they may remain well for many years on optimal medical therapy, the risks of surgery, particularly experimental surgery, in these patients are unacceptable. Subjects in our proposed trial will have already been determined to be good surgical candidates for DBS, and we propose to piggy-back on the DBS surgery to minimize risk (no additional invasive

surgery). This will also more rigorously test the benefits of our therapy, since this approach will provide for a control group which will be receiving a comparably invasive therapeutic intervention (DBS/saline vs. DBS/gene therapy), as opposed to an ethically contentious sham surgery. Specifically, we will transfer the gene for an enzyme, called GAD, which is responsible for synthesizing the major inhibitory neurotransmitter in the brain, GABA. GABA will be produced and released in a brain region where based on drug infusion studies in humans with PD, and many experimental animal studies, it is likely to improve Parkinsonian symptoms. This brain region is called the subthalamic nucleus (STN) and is a very small brain region, only a few millimeters in each dimension, but it plays a central role in the brain's circuit of cells responsible for regulating movement as we discussed above. Experience worldwide in over 200 patients has shown that electrical silencing of the STN achieved by DBS results in dramatic improvement in most parkinsonian symptoms (notable exceptions being cognitive decline as well as voice and speech which are only partially improved). The gene transfer of GAD may provide similar benefit and it is therefore reasonable to question why we are using a non-curative strategy of unknown risks when STN DBS is so effective. There are two major advantages of our approach compared to DBS. Firstly, DBS is associated with significant morbidity, up to 50% of patients have significant side-effects, many of them very serious and the vast majority due to the implanted device, and the necessity to perform part of the surgery under general anesthesia. Our gene transfer approach may be carried out exclusively under local anesthesia and leaves no hardware in place. This should minimize risks of infection, erosions, device migration, disconnects and hardware failures, as well as complications of general anesthesia. The second advantage is more theoretical, but is based on our experimental data in rodent models of PD showing that the GAD gene transfer is not only likely to match DBS in symptom reduction, but it may also slow down or perhaps even arrest the disease progression. The trial design we are

proposing involves 20 patients, all of whom will receive DBS, but only half will receive GAD gene transfer, the others will have identical procedures, but receive a tiny volume (about a drop) of saline instead into the STN. Neither the surgeon, the patient nor the neurologists will know whether gene therapy or saline is infused into each patient, since the solutions will be marked with a code that will be kept by another investigator until the completion of the study (unless unexpected effects require breaking this code early). This will prevent false improvements due to patient expectations or physician biases. All DBS patients typically wait several weeks or more for programming and activation of the stimulator; here they will consent to delay activation of the DBS for 6 months, providing an opportunity for the "blinded" investigating neurologists to determine the potential efficacy of the gene therapy in addition to the primary endpoint of safety. At the end of the 6 months the code will be broken, and all symptomatic patients will have the DBS activated. It is possible that some patients may be sufficiently improved by the gene transfer that they may elect to have the stimulating electrode removed. The GAD gene has no known specific toxicity, nor is its overexpression likely to result in untoward complications, moreover this intervention has a major safety valve, the surgical destruction (ablation) of the STN is an accepted therapy of PD, such that if any unexpected adverse effect was to occur, the cells which have taken up the foreign gene can be destroyed as part of a therapeutic intervention. Again, this could be performed by burning the area with the stimulating electrode already in place. To our knowledge, this proposal represents the first truly scientific gene or cell therapy study in the brain, with ethical treated and mock-treated comparison groups, which still provides the patient with the same surgical procedure which they would normally receive and should not subject the patient to additional surgical procedures regardless of the success or failure of the study. Hence, we believe that this study has major advantages in terms of both the potential for patient benefit regardless of the success of the study as well as minimizing

risk. This will represent an important first step of gene medicine to help in the treatment of PD and other degenerative brain disorders.